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(54) Title: CORTISTATIN ANALOGS CAPABLE OF BINDING SELECTIVELY TO GROWTH HORMONE SECRETAGOGUE RECEPTORS

(57) Abstract: The peptides of formula (I): Pro-Cys-Xaa-D-Trp-Lys-Xbb-Cys-Lys-NH_2, and their derivatives with metal chelating agents are useful in the treatment of tumours and acromegaly, and to reduce the appetite.

CORTISTATIN ANALOGS CAPABLE OF BINDING SELECTIVELY TO GROWTH HORMONE SECRETAGOGUE RECEPTORS

The present invention relates to cortistatin analogs able to bind selectively to growth hormone secretagogue receptors.

Cortistatin (Nature, 1996, 381, 242-245) is a tetradecapeptide similar to somatostatin, but has a distinct pharmacological and physiological profile (Brain Research Reviews, 2000, 33, 228-241. Although it binds to five subtypes of somatostatin receptors (Naunyn-Schmiedeberg Arch. Pharmacol., 1998, 357,483-489), cortistatin has distinct effects on electrical cortex activity, sleep and locomotor behaviour (J. Neurosci. Res. 1999, 56, 611-619).

Cortistatin also bonds to growth hormone secretagogue receptors (GHS-R), unlike somatostatin (J. Endocrinol. Invest., 2001,24(1), RC1-RC3) and like ghrelin, an endogenous peptide produced in the stomach (Nature, 1999, 402, 656-660) which stimulates the production of growth hormone (J. Endocrinol. Invest., 2000, 23, 493-495), mediated by interaction with GHS-R (J. Clin. Endocrinol. Metab. 2000, 10, 3803-3807).

The existence of specific corticostatin receptors to which the synthetic GHS peptides can bind has been postulated.

Cyclic peptides have now been found which can bind selectively to the cortistatin receptor, and compete with ghrelin binding to GHS-R.

The peptides of the invention have the following general formula I:

Pro-Cys-Xaa-D-Trp-Lys-Xbb-Cys-Lys-NH_2
I----------I

wherein:

Xaa represents a residue of phenylalanine (Phe), tyrosine (Tyr) or pyridyl-alanine (Pal);

Xbb represents a residue of threonine (Thr) or ter-leucine (Tle).

The invention also relates to conjugates of peptides I with metal or radioactive isotope chelating agents for radiotherapeutic or radiodiagnostic use. The chelating agents can be bind to peptides I directly, via covalent bonds with one of the free functional groups present on the amino acid residues of the peptide, e.g. with the amine groups of the lysine residues, or through a bifunctional linker.

Examples of suitable chelating agents which can be bonded directly or via a linker to peptides are the polyazamacrocyclic bifunctional ligands: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (DO3A), [10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (HPDO3A), 4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oic acid (BOPTA), 2-methyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (MCTA), ($\alpha,\alpha',\alpha'',\alpha'''$)-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetracetic acid (DOTMA); the residue of polyaminophosphates, in particular N,N'-bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid (DPDP) and ethylenedinitrilotetrakis(methylphosphonic) acid (EDTP); residues of polyaminophosphonic or polyaminophosphinic acids, in particular 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis[methylene(methylphosphonic)] acid and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis[methylene (methyl-phosphonic)] acid; the residue of natural macrocyclic chelating agents such as texaphyrines, porphyrines and phthalocyanines; diethylenetriaminepentaacetic acid (DTPA) and its derivatives such as N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]L-glutamic acid (DTPA-GLU), DTPA conjugated with Lys (DTPA-Lys), N-[2-[bis(carboxymethyl)amino]-3-(4-ethoxyphenyl)propyl]-N-[2-[bis(carboxymethyl)amino]ethylglycine (EOB-DTPA), N,N-bis[2-[(carboxymethyl)[(methylcarbamoyl)methyl]amino]ethyl]glycine (DTPA-BMA); N3S triamidothiols, N2S2 diamidodithiols, N4 tetramines,

2-hydrazine-nicotinic acid, and bis amino bisthiol chelating agents (BAT). The structural formulas of these known chelating agents and conjugation and radiolabelling techniques are described in Current Medicinal Chemistry, 2000, 7, 871-994, the contents of which are incorporated here by reference.

Suitable bifunctional linkers include bis-succinimidylmethyl ether (BSME), 4-(2,2-dimethylacetyl)-benzoic acid (DMBA), bis-succinimide-hexane (BSH), tris(succinimidylethyl)amine (TSEA), and similar derivatives having succinimide, thio, carboxy or amine groups.

Peptides I conjugated to chelating agents form stable complexes with the bi- and trivalent ions of radioactive metal isotopes (^{99m}Tc, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{72}As, ^{111}In, ^{113}In, ^{90}Yt, ^{97}Ru, ^{82m}Rb, ^{62}Cu, ^{64}Cu, ^{52}Fe, ^{52m}Mn, ^{140}La, ^{175}Yb, ^{153}Sm, ^{166}Ho, ^{149}Pm, ^{177}Lu, ^{142}Pr, ^{159}Gd, ^{212}Bi, ^{47}Sc, ^{149}Pm, ^{67}Cu, ^{111}Ag, ^{199}Au, ^{188}Re, ^{186}Re, ^{161}Tb and ^{51}Cr), which complexes are also part of the invention.

Peptides of formula I can be used to treat disorders in which a selective interaction with the cortistatin receptor is desirable. In particular, peptides I have proved useful as appetite suppressants, and can therefore be used to treat obesity, excess weight and acromegaly. The radiolabelled conjugates of peptides I can be used for the treatment and/or diagnosis of tumours which express the cortistatin receptor and GH-dependent tumours such as cancer of the lung, breast, thyroid, pancreas, pituitary gland and other tissues that express GHS-R.

For the proposed therapeutic and diagnostic uses, the peptides or conjugated and labelled peptides of the invention will be formulated in formulations suitable for oral, parenteral or transmucosal (sublingual, intranasal or rectal) administration.

Examples of suitable formulations for parenteral administration include sterile aqueous solutions or suspensions with pH values between approximately 6.0 and 8.5, and peptide concentrations ranging between 0.001

and 1.0 molar.

These formulations may be freeze-dried and supplied as such, ready to be reconstituted at the time of use.

Examples of suitable formulations for oral administration include tablets and capsules, possibly gastro-protected, syrups, effervescent granules, solutions and suspensions.

The doses can range widely, depending on the pharmacokinetic and toxicological characteristics of the peptide chosen and the disorder in question. As a rule, the appropriate dose will be approx. 0.1 μg to 10 μg of total peptide per kg of body weight per day by the parenteral route and approx. 30 μg to approx. 1000 μg of polypeptide per kg of body weight per os in one or more administrations. In the case of radiolabelled peptides, the dose will be determined by the dose of radioactivity required for the specific diagnostic or therapeutic application, in accordance with known parameters depending on the specific activity of the conjugate, the half-life of the radioisotope and the characteristics of the ligand.

The peptides of the invention can also be advantageously formulated in controlled-release compositions, for example as disclosed in EP-A-0858323.

The peptides of the invention can be obtained by conventional methods, for example by solid-phase peptide synthesis.

Solid-phase peptide synthesis starts from the C-terminal end of the peptide. A suitable starting material can be prepared, for example by attaching the required protected alpha-amino acid to a chloromethylated resin, a hydroxymethylated resin, a benzhydrylamine resin (BHA), or a para-methylbenzhydrylamine resin (p-Me-BHA). One of these chloromethylated resins is manufactured by BioRad Laboratories, Richmond, California, and sold under the trademark BIOBEADS SX 1. The preparation of the hydroxymethyl resin is described by Bodansky et al., Chem. Ind. (London) 38,

15997, (1966). BHA resin has been described by Pietta and Marshall, Chem. Comm., 650 (1970), and is marketed by Peninsula Laboratories Inc., Belmont, California.

After the initial attachment, the alpha-amino acid protective group can be removed with a choice of acid reagents, including trifluoroacetic acid (TFA) or hydrochloric acid (HCl) in a solution of organic solvents at room temperature. After removal of the alpha-amino acid protective group, the remaining protected amino acids can be coupled step by step in the desired order. Each protected amino acid can generally be reacted in an excess of approximately three times using a suitable carboxyl activator group such as dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide (DIC) in a solution of methylene chloride (CH_2Cl_2) or dimethylformamide (DMF), and mixtures thereof, for example. When the desired amino acid sequence has been completed, the desired peptide can be cleaved from the supporting resin by treatment with a reagent such as hydrogen fluoride (NF) which not only cleaves the peptide from the resin, but also cleaves the most common protective groups of the side chains. When a chloromethylated or hydroxymethylated resin is used, the treatment with HF gives rise to the formation of the acid peptide in free form. When a BHA or p-Me-BHA resin is used, the HF treatment directly gives rise to the peptide amide in free form.

The solid-phase procedure discussed above is known to the prior art, and was described by Atherton and Sheppard, Solid Phase Peptide Synthesis (IRL Press, Oxford, 1989).

Some methods in solution, which can be used to synthesise the peptide portions of this invention, are specified in Bodansky et al., Peptide Synthesis, 2nd edition, John Wiley & Sons, New York, N.Y. 1976, and by Jones, The Chemical Synthesis of Peptides, (Clarendon Press, Oxford, 1994).

The following examples illustrate the invention in greater detail.

EXAMPLE 1

The peptide of formula:

Pro-Cys-Tyr-D-Trp-Lys-Thr-Cys-Lys-NH_2
I----------I

synthesised on solid phase, has the following characteristics in acetate form:

Mass spectrum: M+ 1025.3

Solubility: 0.2 mg/ml in distilled water.

HPLC titre: 99%

Amino acid analysis: conforming.

EXAMPLE 2

The peptide of formula:

Pro-Cys-Phe-D-Trp-Lys-Thr-Cys-Lys-NH_2
I----------I

synthesised on solid phase, has the following characteristics in acetate form:

Mass spectrum: M+ 1009.2

Solubility: 0.4 mg/ml in distilled water.

HPLC titre: 95%

Amino acid analysis: conforming.

EXAMPLE 3 – Binding studies

The studies carried out on the binding of the peptide described in Example 1 (Tyr^3-cortistatin-8) and Example 2 (cortistatin 8) to GHS-R in human pituitary gland tissue were performed by comparison with cortistatin 14, somatostatin 14 and ghrelin 28, as described in J. Endocrinol. 1998, 157, 99-106 and in J. Endocrinol. Invest., 2001, 24, RC2, using ^{125}I-Tyr^4-ghrelin as ligand.

The results are shown in the annexed Figures 1a-c.

The IC_{50} calculated for the peptides of the invention ranged between 24 and 33 nM, those of ghrelin-28 between 7.5 and 9.5, and those of cortistatin 14 between 11.6 and 14, while those of somatostatin always exceeded 1000

nM.

EXAMPLE 4 - Effect on food consumption.

The peptide described in example 2 was administered subcutaneously at the dose of 300 mcg/Kg to Sprague-Dawley rats weighing approx. 200-250 g, whose appetite was stimulated by subcutaneous injection with 80 mcg/Kg of the peptide GHS Hexarelin.

The animals were also treated in accordance with a crossover protocol with Hexarelin only or with saline, and their food consumption was recorded hourly for the six hours following the treatment, as described in European J. Endocrinol., 2001, 144, 155-162.

Total food consumption was 0.86 ± 0.28 g for the treatment with saline, 0.85 ± 0.19 g for the treatment with Hexarelin associated with the peptide described in Example 2, and 3.33 ± 0.47 g for the treatment with Hexarelin only.

CLAIMS

1. Peptides of formula I

Pro-Cys-Xaa-D-Trp-Lys-Xbb-Cys-Lys-NH_2
I----------I

I

wherein

Xaa represents a residue of phenylalanine (Phe), tyrosine (Tyr) or pyridyl-alanine (Pal);

Xbb represents a residue of threonine (Thr) or ter-leucine (Tle).

2. Peptides as claimed in claim 1, wherein Xaa is Tyr.

3. Peptides as claimed in claim 1, wherein Xaa is Phe.

4. Peptides as claimed in claim 1, wherein Xbb is Thr.

5. A peptide as claimed in claim 1, selected from:

Pro-Cys-Phe-D-Trp-Lys-Thr-Cys-Lys-NH_2
I----------I

Pro-Cys-Tyr-D-Trp-Lys-Thr-Cys-Lys-NH_2
I----------I

6. Conjugates of the peptides as claimed in claims 1-5 with metal or radioactive isotope chelating agents, and the corresponding chelated complexes of the said metals or isotopes.

7. Conjugates as claimed in claim 6, wherein peptides I are bonded to the chelating agent directly via covalent bonds with one of the free functional groups present on the amino acid residues of the peptide, or via a bifunctional linker.

8. Chelated complexes as claimed in claim 6 or 7 of metals selected from ^{99m}Tc, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{72}As, ^{111}In, ^{113}In, ^{90}Yt, ^{97}Ru, ^{82m}Rb, ^{62}Cu, ^{64}Cu, ^{52}Fe, ^{52m}Mn, ^{140}La, ^{175}Yb, ^{153}Sm, ^{166}Ho, ^{149}Pm, ^{177}Lu, ^{142}Pr, ^{159}Gd, ^{212}Bi, ^{47}Sc, ^{149}Pm, ^{67}Cu, ^{111}Ag, ^{199}Au, ^{188}Re, ^{186}Re, ^{161}Tb and ^{51}Cr.

9. Pharmaceutical or diagnostic compositions containing one of the peptides as claimed in claims 1-5 or one of the chelated complexes as claimed in claims 6-8, mixed with a suitable vehicle.

10. Pharmaceutical compositions as claimed in claim 9, with controlled release.

11. Use of the peptides as claimed in claims 1-5 or the chelated complexes as claimed in claims 6-8 for the preparation of medicaments for the treatment of tumours and acromegaly and to reduce the appetite.

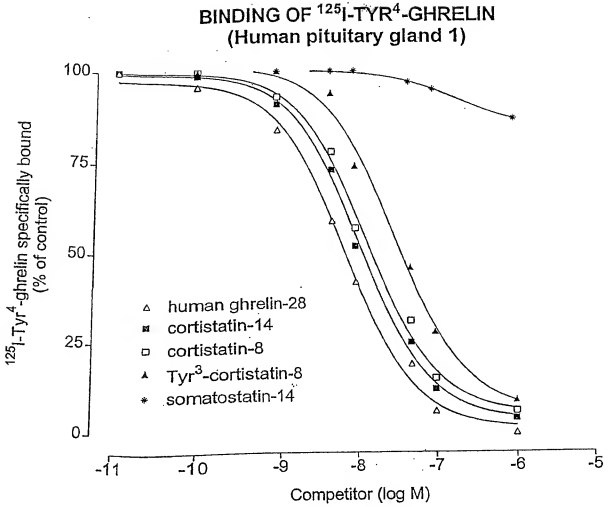
BINDING OF 125I-TYR4-GHRELIN
(Human pituitary gland 1)
125I-Tyr4-ghrelin specifically bound
(% of control)
100
75
50
25
0
human ghrelin-28
cortistatin-14
cortistatin-8
Tyr3-cortistatin-8
somatostatin-14
-11
-10
-9
-8
-7
-6
-5
Competitor (log M)

Fig. 1a

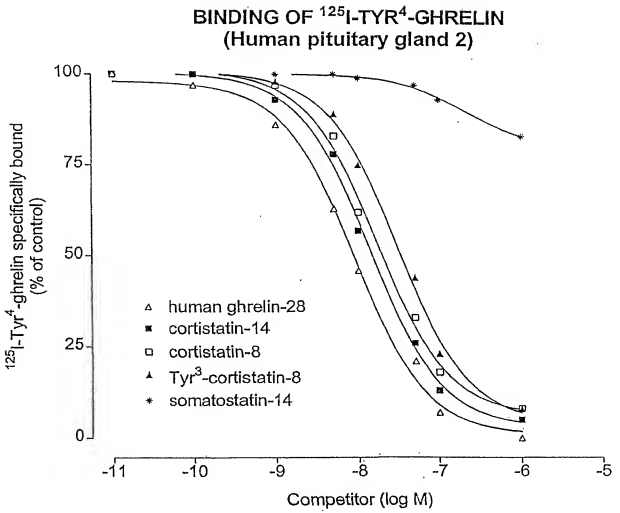
BINDING OF 125I-TYR4-GHRELIN
(Human pituitary gland 2)
125I-Tyr4-ghrelin specifically bound
(% of control)
100
75
50
25
0
human ghrelin-28
cortistatin-14
cortistatin-8
Tyr3-cortistatin-8
somatostatin-14
-11
-10
-9
-8
-7
-6
-5
Competitor (log M)

Fig. 1b

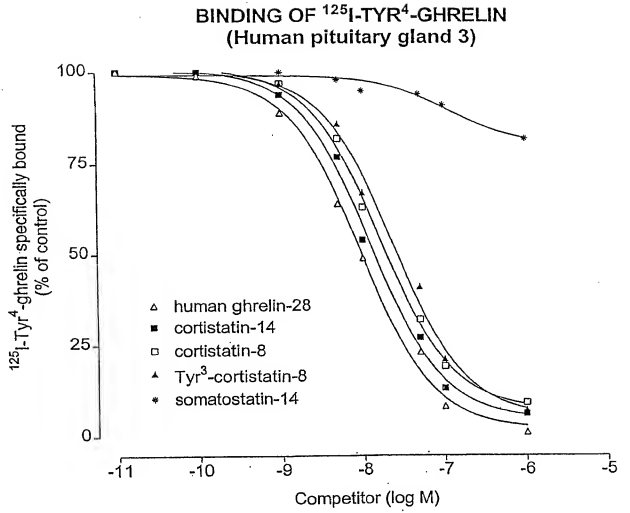
BINDING OF 125I-TYR4-GHRELIN
(Human pituitary gland 3)
125I-Tyr4-ghrelin specifically bound
(% of control)
100
75
50
25
0
-11
-10
-9
-8
-7
-6
-5
Competitor (log M)
human ghrelin-28
cortistatin-14
cortistatin-8
Tyr3-cortistatin-8
somatostatin-14

Fig. 1c

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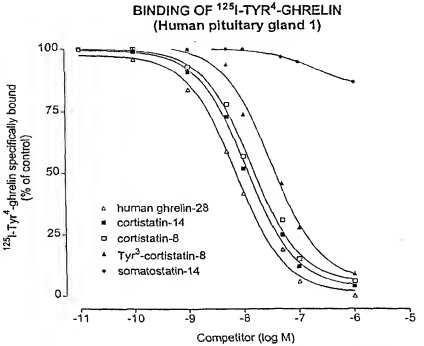

(57) Abstract: The peptides of formula (I): Pro-Cys-Xaa-D-Trp-Lys-Xbb-Cys-Lys-NH_2, and their derivatives with metal chelating agents are useful in the treatment of tumours and acromegaly, and to reduce the appetite.

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INTERNATIONAL SEARCH REPORT

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SPIER AVRON D ET AL: "Cortistatin: A member of the somatostatin neuropeptide family with distinct physiological functions." BRAIN RESEARCH REVIEWS, vol. 33, no. 2-3, September 2000 (2000-09), pages 228-241, XP002224723 ISSN: 0165-0173 the whole document --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lüdemann, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; January 2001 (2001-01) DEGHENGHI R ET AL: "Cortistatin, but not somatostatin, binds to growth hormone secretagogue (GHS) receptors of human pituitary gland." Database accession no. PREV200100128359 XP002224725 abstract & JOURNAL OF ENDOCRINOLOGICAL INVESTIGATION, vol. 24, no. 1, January 2001 (2001-01), pages RC1-RC3, ISSN: 0391-4097 ---	1-11
A	PAPOTTI MAURO ET AL: "Growth hormone secretagogue binding sites in peripheral human tissues." JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 85, no. 10, October 2000 (2000-10), pages 3803-3807, XP002224724 ISSN: 0021-972X the whole document -----	1-11